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(54) Title: ANTIMICROBIAL COMPOSITIONS

(57) Abstract: The invention relates to the use, in an antimicrobial composition comprising (a) an antimicrobially effective amount of a dissolved antimicrobial metal ion and (b) a dissolved halide ion present in a molar excess relative to the metal ion, of a sufficient excess of the halide ion to stabilise the antimicrobial activity of the metal ion against loss on exposure to light and gamma radiation.

ANTIMICROBIAL COMPOSITIONS

Field of the Invention

The present invention relates generally to antimicrobial agents and, in particular, to stabilized, metal-based antimicrobial agents suitable especially for topical applications in the prevention and treatment of infections and as a treatment for medical devices to make them infection resistant.

Background of the Invention

Antimicrobial agents are chemical compounds and compositions that inhibit microbial growth or kill bacteria, fungi and other microorganisms. The antimicrobial activity of inorganic substances is generally related to the ions into which they dissociate. The antimicrobial activity of various metal ions, for example, is often attributed to their affinity for protein material and the insolubility of the metal proteinate formed. Metal-containing salts are thus examples of inorganic substances that act as antimicrobial agents.

Infection is a common complication associated with the use of medical devices. Various techniques have been described that incorporate potentially toxic metal ions in the form of metal salts into the materials which make up these medical devices.

For example, U.S. Pat. No. 4,603,152, the disclosure of which is incorporated herein by reference, describes an antimicrobial composition useful in providing antimicrobial coatings on medical devices. In this composition, particles of antimicrobial metal compounds are mixed in a polymer matrix and coated onto a medical device to provide antimicrobial protection on that device.

U.S. Pat. No. 4,054,139, the disclosure of which is incorporated herein by reference, describes a catheter wherein the exterior and interior surfaces of the catheter have fixed and exposed thereon an effective quantity of silver-bearing, immobile, oligodynamic material which provides the catheter with antimicrobial

protection.

A major shortcoming of these techniques relates to the poor solubility and consequent slow surface diffusion of the metal salt in the hydrophic and lipophilic material matrix that makes up the medical devices. Indeed, because the antimicrobial metal salt must be on the surface of the medical device, the antimicrobial protection of the medical implant will last only as long as the metal-salt or compound is on the surface. Additionally, the metal ion is generally not photostable, and upon exposure to light is reduced to a metal, thereby losing antimicrobial efficiency.

If, on the other hand, metal salt compounds are added to a separate polymer composition which is then used to coat the surface of the medical device, a problem arises because the coating of an implant with a separate polymer composition may change the dimensions of the medical device. Although this may not be important to medical devices such as wound dressings, a change in size of a medical implant such as a catheter may affect its usefulness.

In U.S. Pat. No. 4,581,028, the disclosure of which is incorporated herein by reference, Fox describes a method for making infection-resistant polymeric implants by treating the implant first with an aqueous solution of a sulfonamide salt, and then with an aqueous solution of a silver salt such as silver nitrate. Fox appears to consider that the silver ion will chelate to the sulfonamide anion on the surface of the polymer and this would provide longer lasting antimicrobial efficacy than would simple treatment of the implant with silver nitrate solution, because the silver-sulfonamide salt would solvate into the surrounding environment more slowly.

Romans, in U.S. Pat. No. 3,092,552, the disclosure of which is incorporated herein by reference, discloses the use of silver ion as an oligodynamic agent in a therapeutic or surface-treating composition or as an effective means for germicidally protecting an article or surface. Specifically, the disclosed composition is comprised of a low concentration of a silver compound such as silver nitrate or silver oxide, a reducing agent such as starch or sugar, polyethylene glycol (PEG)

and urea. This patent further teaches the addition of small amounts of sodium chloride or cupric chloride to the composition, to prevent discoloration even when the product is exposed to sterilization procedures and direct sunlight. The presence of metal ions such as copper and/or zinc is considered to stabilize the silver ion, making it more selective in its germicidal activity. Although Romans teaches that the quantities of these metals in the composition should vary, he states that the ratio of copper and/or zinc to silver should be no greater than 2:1.

Another reference teaching pharmaceutical compositions comprised of polyethylene glycol, a metal cation and an anion, is Kaplan, U.S. Pat. No. 4,451,447, the disclosure of which is incorporated herein by reference. Specifically, this reference teaches a composition comprised of cisplatin, PEG and a source of chloride ion, such as sodium chloride, for use in treating human neoplasms. Kaplan teaches that complexation of the cisplatin with PEG prevents crystallization of the cisplatin during storage and thereby maintains pharmaceutical activity. The compositions do not appear to be photostable, in that Kaplan explicitly teaches against exposing the composition to light.

In U.S. Pat No. 5326567, the disclosure of which is incorporated herein by reference, Capelli discloses antimicrobial metal-based compositions - which are said to be photostable, non-staining, and which are easily absorbed into lipophilic matrices - containing silver cations complexed by acyclic polyether polymers through the formation of a "host-guest relationship" where the acyclic polyether is the "host" and the silver cation is the "guest," wherein stabilization of this "host-guest relationship" is accomplished through the use of excess halide anions. The compositions are stated to be useful for topical treatment of infections caused by bacteria, fungus and viruses in humans and animals and for treating medical devices and adhesives to impart infection-resistance. However, we have found that Capelli's formulations are not suitable for incorporation into hydrophilic polymeric matrices such as hydrogels (e.g. sheet hydrogels, shaped hydrogels for example contact lenses, or hydrogel foam compositions), in that the resultant hydrogels do not have stability to gamma radiation and have to be carefully formulated to have light stability. To provide effective stability to gamma radiation and light, the amount

of silver ion present in the hydrogel would have to be made very small, damaging the antimicrobial effectiveness of the composition.

Hydrogel compositions, e.g. for use in wound, burn and other dressings, are increasing in their use, due to their ability to provide moist healing environments. Such hydrogels may typically contain from about 2 to 80 or more % by weight of water. There is a continuing need for hydrogels which are resistant to microbial growth and are generally hostile to microorganisms such as bacteria, fungi and viruses. However, there is also a need for these dressings to be light and radiation stable, as radiation is typically applied in the polymerization procedure during manufacture. Hitherto, the requirement of radiation stability has limited the use of silver ions as an antimicrobial agent in hydrogel compositions.

Brief Description of the Invention

We have now surprisingly found that the stabilizing acyclic polyether required in Capelli's formulations are not necessary for producing light stable formulations. We have particularly discovered an antimicrobial agent suitable for incorporation into an aqueous composition such as, for example, a hydrogel, to impart to the composition an antimicrobial activity which is photostable and radiation stable, by using antimicrobial metal ions (e.g. silver ions) in the presence of a molar excess (relative to the metal ions) of halide ions, for example chloride. Preferably, a substantial molar excess, e.g. around 500 fold excess, of halide ions is used.

We have further discovered that the inclusion of an acyclic polyether in the compositions of the present invention, leads to a decrease in the photostability and radiation stability. We have also surprisingly found that antimicrobial agents of the present invention are readily incorporated into hydrogel compositions such as, for example, sheet hydrogels, shaped hydrogels, amorphous hydrogels and foamed hydrogels

In one aspect the present invention provides photostable and radiation stable antimicrobial metal compositions useful in the treating infection and useful in preventing infection.

In another aspect the invention provides hydrogel compositions, for example sheet hydrogels, shaped hydrogels, amorphous hydrogels and foamed hydrogels, which are photostable and radiation stable possessing antimicrobial properties useful in the treating of infection and useful in preventing infection.

In a further aspect the invention provides a manufacturing process whereby hydrogel compositions stable to light and radiation are made by photopolymerisation.

In a further aspect the invention provides a manufacturing process whereby hydrogel compositions stable to light and radiation are made by radiation (for example electron beam and/or gamma) induced polymerization.

According to one aspect of the present invention, there is provided an antimicrobial agent, wherein the antimicrobial activity is stable against both light and radiation, comprising an effective amount of antimicrobial metal (e.g. silver) ions and stabilizing halide ions, wherein the halide is present in an excess with respect to the amount of metal ions.

The invention further provides compositions comprising the above antimicrobial agent for the treatment of infection in mammals or for providing antimicrobial protection to medical devices, wound dressings, sutures and other objects at risk of microbial infection (e.g. infection by bacteria, viruses or fungi). The compositions may, for example, be hydrogels or other pharmaceutical compositions including further pharmacologically acceptable carriers or diluents.

The compositions may be adhesive, e.g. adhesive to the skin (particularly, human skin).

The agent and compositions according to the present invention are distinguished from those described in US Patent No. 5,326,567, in that they have stability to gamma radiation. It is preferred that the agent and compositions according to the present invention are used in the effective absence of acyclic polyethers, to assist

gamma stability. It is particularly preferred that the agent and compositions according to the present invention consist essentially of the metal and halide ions as the antimicrobially active component and stabilizer, with less than about 10%, particularly less than about 5%, by weight of any other antimicrobially active agent or stabilizer therefor.

The antimicrobial agent according to the present invention is preferably present as solvated ions in intimate admixture in solution, particularly in aqueous solution. The solution is preferably entrained in a suitable reservoir or carrier such as the hydrogel compositions mentioned above.

The present invention further provides a method of treating or preventing infection in a mammal, e.g. a human, in need thereof, comprising the step of administering to the mammal an antimicrobially effective amount of the agent or composition according to the present invention.

Detailed Description of the Invention

The present invention relates to antimicrobial metal-based agents and compositions which are photostable, radiation stable and easily incorporated into hydrogel matrices.

The antimicrobial metal-based agents and compositions are preferably obtained by a method comprising forming a solution of the antimicrobial metal cation in the presence of excess halide anions and an amount of solvent. The solvent may be aqueous (water), organic or a mixture thereof, provided that the necessary ionic availability is achieved. In the case of solvent being water, the "water activity" - as defined by the equivalent relative humidity (ERH) of the halide solution into which the silver is dispersed – should preferably not exceed 75%.

The preferred metal-based antimicrobial agents and compositions of the present invention have at least the following components:

(a) silver ions; and

(b) an excess of halide ions relative to the concentration of the silver ion.

The molar halide excess should preferably be greater than 450, more preferably greater than 500.

To obtain large molar excesses of halide (for example, chloride), highly water soluble halide salts are required. The expression "highly water soluble" generally means that the salt in question forms at 20°C a saturated solution in water which has a concentration substantially greater than 0.1M, e.g. greater than about 1M or greater than about 2M. The use of salt solutions of monovalent metals, such as sodium chloride or potassium chloride, is not desirable as highly concentrated solutions are required to provide sufficient halide ion. These solutions are close to, or exceed saturation, and are of limited use - especially when the antimicrobial metal based composition is to incorporated into for example another matrix, for example a hydrogel.

Preferred halide solutions are solvated forms of halide salts of multivalent cations such as, for example, calcium or magnesium or quaternary ammonium salts. Preferred salts are magnesium chloride and calcium chloride and the chlorides of quaternary ammonium salts. Preferred quaternary ammonium chloride salts are substituted vinyl compounds such as monomers or polymers. Examples include acryloyloxyethyltrimethyl ammonium chloride (DMAEA-Q, Kohjin) and acrylamidopropyltrimethyl ammonium chloride (Kohjin) and polymers and copolymers derived from them.

We have found that in order to obtain light and radiation stable silver salt solutions a molar excess of chloride ion greater than 450 times that of the silver ion concentration, and even more preferably greater than 500 times, is required. Further, the water activity of the solution into which the silver salt is dissolved must not exceed about 75% (ERH, as measured by a water activity meter, for example) and preferably is less than about 70%. It will be appreciated by those skilled in the art that the terms osmolality, isotonicity, hyper-tonicity and hypo-tonicity are alternative descriptions of the water activity in the solution or material and hence are to be considered equivalent.

The silver ions are preferably the solvated ions derived from a soluble silver salt, for example silver nitrate, silver acetate, silver sulphate or silver lactate, preferably silver nitrate. The silver ions are present in the stable salt solution at antimicrobially effective concentrations, according to the manner in which the material/solution is to be applied to the medical device or topically to the body. The effective amount is typically from about 0.01 to about 0.5% by weight of the solution.

In the following description, the invention will be described with reference to silver ion as the antimicrobially effective metal ion. However, the description should be understood to refer equally to other antimicrobially effective metal ions.

The stabilized silver salt solution (herein: SSSS) may be diluted with water, or aqueous liquids or solutions or other compounds soluble in the SSSS (such that the water activity does not exceed about 75% ERH). Polyhydric alcohols, for example glycerol or sorbitol, may be used as diluents. Polyethylene glycols have been found to destabilize the SSSS, and should preferably not be used.

We have discovered that the SSSS may be readily incorporated in to many different types of hydrogel (also including hydrocolloids) and impart excellent antimicrobial properties (as determined by USP 25/2000 Antimicrobial Preservative Effectiveness). The hydrogels are polymerized monomers, which may be homopolymers or copolymers and may, for example, be based on ionic (cationic, anionic, amphoteric or zwitterionic) monomers and comonomers, non-ionic monomers and comonomers, or any combination or mixture thereof. The hydrogels are preferably cross-linked. Examples of relevant chemistries and hydrogels can be found in published PCT patent applications nos. PCT/GB99/02505 and PCT/GB00/00302, the contents of which are incorporated herein by reference.

Examples of anionic monomers include the sodium or potassium salt of acrylic acid or methacrylic acid, the sodium or potassium salt of 3-sulphopropyl acrylate (SPA) or the corresponding methacrylate, and the sodium or potassium salt of 2-

acrylamido-2-methylpropane sulphonic acid (NaAMPS), or any combination or mixture thereof, including mixtures of any two or all three.

A cationic monomer is preferably either a quaternary ammonium salt derivative of acrylic acid/methacrylic acid or a quaternary ammonium salt derivative of an N-substituted acrylamide or combinations of both. Preferred examples include acryloyloxyethyltrimethyl ammonium chloride (DMAEA-Q, Kohjin), acryloyloxyethyltrimethyl ammonium methyl sulphate (Aldrich), acrylamidopropyltrimethyl ammonium chloride (Kohjin).

Copolymers comprising both anionic and cationic monomers may also be useful. When the molar ratios of cationic and anionic monomers are unity, the resulting hydrogel may exhibit amphoteric behaviour (the hydrogel swells more in salt solution than in pure water).

A non-ionic monomer may, for example, be selected from acryloyl-morpholine (ACMO), e.g. N-acryloylmorpholine, 1-acryloylmorpholine, or 2-acryloylmorpholine; an acrylamide; an N-substituted acrylamide; an acrylic/methacrylic acid; a vinyl lactam; and N-vinylpyrrolidone.

The hydrogel composition is preferably formed in generally conventional manner, by polymerising a mix (the "pre-mix"). The total amount of monomer or co-monomer present in the pre-polymerisation mix (e.g. for making a film) is about 1-60%, preferably about 10-45%, preferably about 20-45%, by weight of the total composition, such that the molar ratio of anionic to cationic monomer is preferably from about 0.8 to about 1.2, preferably about 0.9 to about 1.1, preferably about 0.95 to about 1.05 and more preferably about 1. The balance of the composition preferably comprises the stabilised silver salt solution, water (preferably about 2 to about 80%, preferably about 5 to about 60%, by weight of the total mix), a polyhydric alcohol (0 to about 50%, preferably about 10 to about 40%, by weight, where the polyhydric alcohol is preferably glycerol (Aldrich)), a cross-linking agent (preferably about 0.04% to about 5 %, preferably about 0.06 to about 0.3%, by weight, where the preferred cross-linking agent is polyethylene glycol di-acrylate (Aldrich)), optionally a photo-initiator (Darocure 1173 or Irgacure 184 or any

combination thereof; preferably 0.001% to about 0.1% by weight), and optional additional ingredients, such as, for example, medicaments, adhesion promoters or surfactants (e.g. 0% to about 10% by weight total of such optional additional ingredients).

The hydrogel can be made in generally conventional manner by casting the pre-polymerisation mix on to a suitable substrate (for example, a sheet, film, non-woven sheet, film or tube, which may be formed from any suitable material, for example a synthetic or natural polymer or a ceramic material), and curing the mix. Curing may, for example be effected with the aid of light (preferably UV). The pre-polymerisation mix may alternatively be cured with the aid of an electron beam or ionising radiation, for example gamma. In these cases the photo-initiator is not required. A thermal initiator may be substituted for the photo-initiator and the pre-mix alternatively cured by means of heat.

From the assembly of the pre-polymerisation mix a continuous film may be made by coating the mix onto a substrate (which is preferably siliconised for easy release), which may be a polymer such as polyester, polyethylene, polypropylene, polyurethane, or paper, or a web, net, foam or a non-woven material, e.g. made from natural and/or synthetic materials. The coated substrate is then cured, e.g. by being passed under a UV light. After curing a siliconised cover is preferably placed on top of the exposed surface of the hydrogel. The thickness of the hydrogel film can typically be from about 0.05mm to about 3mm.

A foamed hydrogel of the present invention comprises a cellular structure within the bulk of the hydrogel material, preferably extending also to the surface of the material. Such a hydrogel can suitably be made by mechanically agitating the premix and then coating the agitated (aerated) pre-mix onto a substrate (web) as for the film. The foam so formed can be porous throughout its thickness or can be coated such that a composite structure of film supporting a foam can be made. The thickness of the foam or film foam structure can typically be from about 0.1mm to about 3mm.

Pre-made hydrophilic polymers/copolymers and mixtures thereof, natural and/or synthetic, may be added to the premix in an amount up to about 10% by weight. Pre-made hydrophilic polymers, copolymers and mixtures thereof may also be used in place of the monomers and crosslinked by means of light, ionising radiation or electron beam.

Examples

The following non-limiting examples are included for further illustration of the present invention, without limitation.

General Preparative Method

A stabilised silver salt solution was made by first making an aqueous solution of the stabilising salt and adding a 1M aqueous silver nitrate solution according the amounts specified in the following pre-polymerisation formulations. The pre-polymerisation formulations were assembled as described in, for example, PCT patent applications nos. PCT/GB99/02505 and PCT/GB00/00302. PI/XL refers to the total amount of photoinitiator (Darocur1173) and crosslinker (polyethylene glycol di-acrylate (IRR 280, UCB)) used per 100g of formulation. The ratio of photoinitiator to crosslinker is typically 4/20.

Examples 1-8

	1	2	3	4	5	6	7	8
CaCl2 %	11	25	25.15	25	25	25.14	25	25
AgNO3 %	0.049	0.14	0.11	0.11	0.11	0.11	.11	0.11
Water %	22.0	25.41	30.15	40.15	50	30.2	30.07	30.46
GLYCEROL %	49.5	0	0	0	0	4.9	10.01	14.74
ACMO %	17.451	49.45	44.59	34.74	24.89	40.65	34.81	29.69
Total	100	100.	100	100	100	100	100	100.1184
pi/xl g/100g	0.54	0.25	0.3	0.25	0.35	0.3	0.3	0.3
Comments	Cloudy solution, went grey under uv light,	Clear colourless very tough gel	Clear colourless very tough gel	Clear colourless very tough gel	Clear gel -.	Clear colourless tough gel	Clear colourless tough gel	Clear colourles s tough gel

Examples 9-13

	9	10	11	12	13
%WATER	28	25.7	27.9	25.77	25.63
% $MgCl_2$	7.8	7.6	7.5	7.65	7.58
%$Ag(NO_3)$	0.045	0.044	0.049	0.044	0.044
%Glycerol	48	47.37	48.1	37.68	37.73
% NaAMPS	16.155	0	16.451	0	0
%SPA	0	19.256	0	28.856	29.016
Total	**100**	**100**	**100**	**100**	**100**
PI/XL g/100g	0.44	0.49	0.43	0.5	0.5

Comments	Slight silver darkening - pale grey colour	Soft clear gel	soft clear gel	Firm clear gel	Firm clear colourless gel

Examples 14-16

	14	**15**	**16**
%WATER	29.236	29.91	20.87
% $MgCl_2$	4.26	4.37	0
%$Ag(NO_3)$	0.044	0.044	0.044
%Glycerol	27.09	49.072	49.09
% NaAMPS	21.38	0	0
%DMAEA-Q	17.99	16.604	29.996
	100	100	100
PI/XL g/100g	0.4	0.62	0.55
Comments	Clear colourless tough gel	Clear colourless gel	Clear colourless well cured gel

The foregoing broadly describes the present invention, without limitation. Variations and modifications as will be readily apparent to those skilled in this art are intended to be included within the scope of this application and subsequent patent(s).

CLAIMS

1. An antimicrobial composition comprising (a) an antimicrobially effective amount of a dissolved antimicrobial metal ion and (b) a dissolved halide ion, wherein the halide ion is present in a sufficient excess relative to the amount of the metal ion present to stabilise the antimicrobial activity of the metal ion against loss on exposure to light and gamma radiation.

2. An antimicrobial composition according to claim 1, wherein the ions are dissolved in a solvent comprising one or both of water and an organic polyhydric alcohol.

3. An antimicrobial composition according to claim 2, wherein the organic polyhydric alcohol is glycerol or sorbitol.

4. An antimicrobial composition according to claim 2, wherein the solvent comprises water.

5. An antimicrobial composition according to any one of the preceding claims, wherein the antimicrobial metal ion is silver.

6. An antimicrobial composition according to any one of the preceding claims, wherein the halide ion is present in an at least about 450-fold molar excess relative to the metal ion.

7. An antimicrobial composition comprising dissolved halide ion and an antimicrobially effective amount of dissolved silver ion, wherein the halide ion is present in an at least about 450-fold molar excess relative to the amount of the silver ion present.

8. An antimicrobial composition according to claim 7, wherein the ions are dissolved in a solvent comprising one or both of water and an organic polyhydric alcohol.

9. An antimicrobial composition according to claim 8, wherein the organic polyhydric alcohol is glycerol or sorbitol.

10. An antimicrobial composition according to claim 8, wherein the solvent comprises water.

11. An antimicrobial composition according to any one of the preceding claims, wherein the equivalent relative humidity or water activity of the composition does not exceed about 75%.

12. An antimicrobial composition according to any one of the preceding claims, wherein the equivalent relative humidity or water activity of the composition does not exceed about 70%.

13. An antimicrobial composition according to any one of the preceding claims, wherein the halide ion is chloride.

14. An antimicrobial composition according to any one of the preceding claims, wherein the halide ion is present in an at least about 500-fold molar excess relative to the metal ion.

15. An antimicrobial composition according to any one of the preceding claims, wherein the composition is effectively free of other agents for stabilising the antimicrobial activity of the metal ion against light and gamma other radiation.

16. An antimicrobial composition according to any one of the preceding claims, wherein the composition is effectively free of chelating agents for the antimicrobial metal ion.

17. An antimicrobial composition according to any one of the preceding claims, wherein the composition is effectively free of acyclic polyethers complexed with the antimicrobial metal ion.

18. An antimicrobial composition according to any one of the preceding claims, wherein the composition is effectively free of copper and zinc ions.

19. A light-stable antimicrobial hydrogel composition comprising a hydrogel polymer and an antimicrobially effective amount of an antimicrobial composition according to any one of the preceding claims.

20. A hydrogel composition according to claim 19, wherein the hydrogel polymer is selected from polymers formed from monomers selected from: the sodium salt of acrylic acid, the sodium salt of methacrylic acid, the potassium salt of acrylic acid, the potassium salt of methacrylic acid, the sodium salt of 3-sulphopropyl acrylate, the sodium salt of 3-sulphopropyl methacrylate, the potassium salt of 3-sulphopropyl acrylate, the potassium salt of 3-sulphopropyl methacrylate, the sodium salt of 2-acrylamido-2-methylpropane sulphonic acid, the potassium salt of 2-acrylamido-2-methylpropane sulphonic acid, a quaternary ammonium salt of acrylic acid, a quaternary ammonium salt of methacrylic acid, a quaternary ammonium salt of an N-substituted acrylamide, N-acryloylmorpholine, acrylamide, N-substituted acrylamide, acylic acid, methacrylic acid, N-vinyl lactams, N-vinyl pyrrolidone, and any combination thereof.

21. A hydrogel composition according to claim 19 or 20, further comprising one or more other ingredients, preferably in minor amounts compared with the ingredients stated in the said claim 19 or 20.

22. A hydrogel composition according to claim 21, wherein the said one or more other ingredients is selected from: one or more ionic and/or non-ionic compounds, such as medicaments (for example: antiseptics, additional antimicrobial agents, antibiotics, analgesics, anaesthetics), humectants (for example, glycerol, sorbitol), vitamins, adhesion enhancers (for example: vinyl acetate dioctylmaleate copolymers), pH buffers, surfactants and water soluble polymers (for example: polysaccharides and synthetic polymers).

23. A hydrogel composition according to any one of claims 19 to 22, selected from sheet hydrogels, shaped hydrogels, amorphous hydrogels and foamed hydrogels.

24. A hydrogel composition according to any one of claims 19 to 23, further comprising an organic plasticiser or humectant and being bioadhesive.

25. A pharmaceutical composition, preferably for topical application, comprising an antimicrobially effective amount of a composition according to any one of the preceding claims as an active antimicrobial agent.

26. A medical device comprising an antimicrobially effective amount of a composition according to any one of claims 1 to 24 as an active antimicrobial agent.

27. A wound dressing comprising an antimicrobially effective amount of a composition according to any one of claims 1 to 24 as an active antimicrobial agent.

28. A suture comprising an antimicrobially effective amount of a composition according to any one of claims 1 to 24 as an active antimicrobial agent.

29. A method of treating or preventing microbial infection in a human or non-human animal in need thereof, which comprises administering to the human or non-human animal an antimicrobially effective amount of a composition according to any one of claims 1 to 25.

30. A method according to claim 29, wherein the administration is carried out by using a pharmaceutical composition according to claim 25 in a surgical or therapeutic method.

31. A method according to claim 29, wherein the administration is carried out by using a medical device according to claim 26 in a surgical or therapeutic method.

32. A method according to claim 29, wherein the administration is carried out by using a wound dressing according to claim 27 in a surgical or therapeutic method.

33. A method according to claim 29, wherein the administration is carried out by using a suture according to claim 28 in a surgical or therapeutic method.

34. In an antimicrobial composition comprising (a) an antimicrobially effective amount of a dissolved antimicrobial metal ion and (b) a dissolved halide ion present in a molar excess relative to the metal ion, the use of sufficient excess of the halide ion to stabilise the antimicrobial activity of the metal ion against loss on exposure to light and gamma radiation, preferably without the need for non-halide stabilising agents.

35. A use according to claim 34, wherein the composition is a composition according to any one of claims 2 to 24 or is present in a pharmaceutical composition, medical device, wound dressing or suture according to any one of claims 25 to 28.

36. In a photo- and/or gamma-activated polymerisation process for preparing an antimicrobial hydrogel composition comprising a hydrogel polymer and an antimicrobially effective amount of a dissolved antimicrobial metal ion, the use of a sufficient molar excess, relative to the metal ion, of a dissolved halide ion in a polymerisable pre-mix containing the metal ion and to be exposed to light and/or gamma radiation for the said polymerisation, to stabilise the antimicrobial activity of the metal ion against loss on exposure of the metal ion to the said light and/or gamma radiation during the said polymerisation, preferably without the need for non-halide stabilising agents.

37. A use according to claim 36, wherein the composition is a composition according to any one of claims 2 to 24 or is a composition for use in a pharmaceutical composition, medical device, wound dressing or suture according to any one of claims 25 to 28.

INTERNATIONAL SEARCH REPORT

PCT/GB 03/04098

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A01N59/00 A01N59/16 //(A01N59/16,59:00,25:04)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 03 051408 A (MUNRO HUGH SEMPLE ;CERDAN CARINE (GB); FIRST WATER LTD (GB); HOSKI) 26 June 2003 (2003-06-26) the whole document	
X	EP 0 911 297 A (KING JOSEPH A) 28 April 1999 (1999-04-28) example 1	1,2,4,5, 11,13, 15-19, 21,23
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[X] Further documents are listed in the continuation of box C.

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11 December 2003	22/12/2003

Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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